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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,992	10/19/2001	Volkhard Lindner	53689-5006-01	3105

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,992	LINDNER ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 25-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/02 & 3/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group XVIII, claims 23 and 24 in the reply filed on July 26, 2004 is acknowledged.

Claims 1-22 and 25-55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 26, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 23 is dependent on claim 19, which is dependent on claim 13, which is dependent on claim 1. All of the claims that claim 23 are ultimately dependent upon have been withdrawn from consideration as being drawn to a non-elected invention and have not been examined. As the claims that claim 23

are dependent upon are not under examination, it is impossible to fully know the metes and bounds of the claimed method.

In the interests of compact prosecution, the claims of the elected invention have been examined in view of the withdrawn claims in so far as to provide a reasonable interpretation of the invention. The examiner has interpreted claims 23 and 24 to be drawn to a method of treating disease in a human by administering an expression-inhibiting amount of a pharmaceutically acceptable composition comprising an antisense oligonucleotide that has any degree of identity to a nucleic acid encoding any mammalian REMODELIN or a fragment thereof. Applicant must correct the improper dependency upon withdrawn claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

1. Claim 23 is drawn to a method of treating a disease in a human using an antisense molecule directed toward the DNA sequence that encodes mammalian REMODELIN or fragments thereof whereby REMODELIN expression is inhibited. Antisense molecules against the REMODELIN DNA sequence constitute a broad genus of compounds. In order to show possession of a genus, an adequate number of representative species must be disclosed in order to show that the applicant possessed the claimed invention at the time of filing.

2. The specification describes on pages 130-133 the identification and isolation of rat REMODELIN from injured arterial walls and identification of human REMODELIN from sequence homology searching. The specification contemplates using antisense oligonucleotides to inhibit expression of REMODELIN on pages 61-64, contemplates putting antisense oligonucleotides in a vector for the purposes of elucidating mechanisms of action of REMODELIN on pages 72-73 and on pages 108-110 contemplates using antisense oligonucleotides to decrease REMODELIN expression in order to treat a disease condition associated with increased REMODELIN expression. The only disclosed example using antisense sequences to REMODELIN is on page 141, where suppression of REMODELIN expression in MC3T3 cells using a vector containing an antisense to rat REMODELIN is described. There is no description of how to go about identifying antisense sequences to the REMODELIN gene that would function to inhibit expression of the REMODELIN gene in cells associated with a disease characterized by increased levels of REMODELIN gene expression. On pages 91-104 the specification provides general statements regarding physical forms that a

therapeutic composition might have and general methods of delivery. However, there is no description of how to administer such oligonucleotides to a human in such a manner that the oligonucleotide would reach the affected cells in a form and in an amount such that detectable and significant inhibition of REMODELIN expression would occur in order to alleviate a disease state.

3. The instant specification discloses a single sequence (shown in figure 19) defined as an antisense RNA to a nucleic acid encoding REMODELIN, which is not representative of the claimed genus. The specification defines antisense on page 39 to be the non-coding strand of a double stranded DNA encoding a protein that is complementary to the sense strand but does not give any guidance as to the desired size of an antisense oligonucleotide or any defining characteristics beyond complementarity to a portion of the sense strand. Branch describes on page 49, in the paragraph bridging columns 1 and 2, that "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo,* effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells" and that in one report of screening antisense sequences found that "only 3% of the antisense molecules tested in this system were highly effective; 40% had almost no effect." Thus, the specification provides description of one antisense oligonucleotide targeted to a mammalian REMODELIN, but does not provide adequate written description of the entire genus of oligonucleotides capable of effecting antisense inhibition of gene expression. Two isoforms of rat REMODELIN are disclosed but there is no other discussions regarding what would be a fragment of REMODELIN. The

specification contains on page 42 a broad definition of the word fragment that states a fragment of a nucleic acid can be any size from 20-1200 nucleotides or more.

4. The specification lacks adequate description of how to identify antisense molecules to any mammalian REMODELIN or a fragment of any mammalian REMODELIN that would be effective in inhibiting expression of REMODELIN, how to administer them to human beings in an appropriate dose and how to deliver the antisense sequence in a manner so as to effect a modulation of REMODELIN gene expression in a particular tissue or cell. The examples described in the specification describe a single antisense sequence delivered to mouse cells *ex vivo*. The only experiments performed on human cells were immunoblots to define whether REMODELIN was naturally expressed in various types of cells. No experiments were done with antisense sequences delivered to human cells or antisense sequences delivered to any cell in order to treat a disease condition. There is no description that would show the skilled artisan how to treat any disease, including hypertrophic scar formation, in a human using antisense inhibition of REMODELIN expression.

5. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

6. MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

7. With the exception of the antisense sequence and the targeted cells described in the specification, the skilled artisan cannot envision the detailed structure of the encompassed sequences regardless of the complexity or simplicity of the method of isolation. The skilled artisan cannot envision how to identify an antisense sequence that would be effective in decreasing expression of any mammalian REMODELIN, how to deliver an antisense sequence to a human in an amount and via a delivery method that would allow the nucleic to reach the proper cells in an amount that would result in a significant inhibition of the expression of REMODELIN sufficient to alleviate a disease state. Adequate written description requires more than a mere statement that it is part of the

invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

8. Therefore, only the disclosed antisense sequence, but neither the full breadth of the claimed genus of antisense oligonucleotides directed against expression of REMODELIN nor the claimed method of treating a disease in a human with antisense oligonucleotides directed against expression of REMODELIN meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed is not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the

state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

9. Claim 23 is drawn to a method of treating a disease in a human using an antisense molecule directed toward a nucleic acid encoding REMODELIN or a fragment thereof wherein REMODELIN expression is inhibited. Claim 24 designates the treated disease as being hypertrophic scar formation. Methods of gene therapy directed toward inhibition of gene expression in humans are not enabled because of the unpredictability in the art.

10. The state of the art prior art is such that inhibition of gene expression *in vitro* is routine, but *in vivo* inhibition of gene expression at the time of filing and even to the present time is not routine for several reasons, including the problems of delivery, specificity and duration.

11. The specification describes on pages 130-133 the identification and isolation of rat REMODELIN from injured arterial walls and identification of human REMODELIN from sequence homology searching. The specification contemplates using antisense oligonucleotides to inhibit expression of REMODELIN on pages 61-64, contemplates putting antisense oligonucleotides in a vector for the purposes of elucidating mechanisms of action of REMODELIN on pages 72-73 and on pages 108-110 contemplates using antisense oligonucleotides to decrease REMODELIN expression in order to treat a disease condition associated with increased REMODELIN expression.

12. The instant specification discloses a single sequence (shown in figure 19) defined as an antisense RNA to a nucleic acid encoding REMODELIN, which is not representative of the claimed genus. The specification defines antisense on page 39 to be the non-coding strand of a double stranded DNA encoding a protein that is complementary to the sense strand but does not give any guidance as to the desired size of an antisense oligonucleotide or any defining characteristics beyond complementarity to a portion of the sense strand. Thus, the specification provides description of one antisense oligonucleotide targeted to a mammalian REMODELIN, but does not provide adequate written description of the entire genus of oligonucleotides capable of effecting antisense inhibition of gene expression. Two isoforms of rat REMODELIN are disclosed but there is no other discussions regarding what would be a fragment of REMODELIN. The specification contains on page 42 a broad definition of the word fragment that states a fragment of a nucleic acid can be any size from 20-1200 nucleotides or more.

13. The only disclosed example using antisense sequences to REMODELIN is on page 141, where suppression of REMODELIN expression in MC3T3 cells using a vector containing an antisense to rat REMODELIN is described. There is no specific guidance on how to go about identifying antisense sequences to the REMODELIN gene that would function to inhibit expression of the REMODELIN gene in cells associated with a disease characterized by increased levels of REMODELIN gene expression. On pages 91-104 the specification provides general statements regarding physical forms that a therapeutic composition might have and general methods of delivery. However, there is

no specific guidance on how to administer such oligonucleotides to a human in such a manner that the oligonucleotide would reach the affected cells in a form and in an amount such that detectable and significant inhibition of REMODELIN expression would occur in order to alleviate a disease state.

14. The problems of nucleic acid based therapies and antisense technology are well known in the art, particularly with regard to the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, 2000, vol 6, p 72-81), Branch (TIBS 1998, vol. 23, p. 45-50) and Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects.

15. The instant specification discloses the method can be performed by administration of an antisense oligonucleotide via delivery methods including oral, intraocular and topical. None of these delivery methods was routine in the art at the time of filing. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and

concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

16. Opalinska et al. (Nature Review, 2002, vol 1, p. 503-514) state "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

17. Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in humans, with a resultant inhibition of gene expression, as claimed. The specification provides one example of delivery of an antisense oligonucleotide to mouse cells *ex vivo*, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any

organism. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies") states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*In vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

18. Given these teachings, the skilled artisan would not know *a priori* whether introduction of antisense oligonucleotides to humans by the broadly disclosed methodologies of the instant invention, would result in successful inhibition of expression of the target gene. One of skill in the art would not know how to deliver oligonucleotides to a human in such a way that would ensure an amount sufficient to modify or inhibit expression of a target gene is delivered to the proper cell.

19. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are

unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a therapeutic response to a disease.

20. The specification teaches the use of an antisense vector to suppress expression of REMODELIN in one mouse cell line but does not provide the guidance required to overcome the art-recognized unpredictability of using antisense oligonucleotides in therapeutic applications in any organism, including humans. The field of antisense therapeutics does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods. The specification does not provide any specific guidance for overcoming the known unpredictable factors regarding the successful *in vivo* application of antisense.

21. Thus, while the specification is enabling for the delivery of an antisense oligonucleotide to mouse cells *ex vivo* as set forth in the specification, the specification is not enabling for the broad claim of treating a disease associated with an abnormal expression of REMODELIN in a human as the art of inhibiting gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. In order to practice the claimed invention *in vivo* a number of variables would have to be optimized, including 1). determining what sequences would constitute antisense sequences against the DNA sequences encoding all mammalian REMODELIN proteins and what antisense sequences would actually be effective at

inhibiting expression of REMODELIN, 2). the form of the oligonucleotide, whether to use a modified oligonucleotide with one or more backbone, sugar or base modifications, 3). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 4). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the expression of a target gene once it reached the proper cell and 5). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each antisense oligonucleotide. While optimization of any single one of these steps may be routine, when taken together the amount of experimentation becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 23 and 24 are not enabled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Tracy Vivlemore
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Art Unit 1635

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September 10, 2004

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